REMARKS

Pursuant to the entry of the instant amendment, claims 1-6 and 8-14 are presently pending. At the outset, Applicants wish to thank the Examiner for withdrawing the previous grounds of rejection and indicating allowable the subject matter of claims 2-4, 6, 8, and 11. Applicants submit that the instant amendment to claim 1 further distinguishes the present invention from the prior art of record and thereby places the instant application in condition for allowance. In particular, to expedite prosecution, Applicants have herewith amended claim 1 to specify that the stable pharmaceutical formulation of erythropoietin not only contains tris-(hydroxymethyl)-aminomethane as stabilizer, does not contain amino acids or human serum albumin and has a pH ranging from 5.9 to 6.8 but further is phosphate-buffered. Support for this amendment is found in the specification as originally filed, for example at p. 3, lines 12-17, and p. 5, line 11. Accordingly, no new matter has been added.

Applicants respectfully submit that the stable, phosphate-buffered, pharmaceutical formulation of EPO as presently claimed is neither disclosed nor fairly taught by the prior art of record. However, Applicants reiterate that the instant amendment is presented solely for the purpose of expediting prosecution and should not be construed as Applicants agreement with or acquiescence to the grounds of rejection previously set forth.

Turning now to the Final Office Action of July 18, 2008, claims 1, 5, 9-10, and 12-14 stand finally rejected as anticipated or obvious over newly cited base references Ogushi (JP 59078124) and Espada (Biochem. Med., 1970). Applicants respectfully submit that like the previously cited references, the newly cited references fail to disclose or suggest the invention of the presently pending claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections in view of the following remarks:

Rejections under 35 U.S.C. § 102

Ogushi et al.:

Claims 1, 5, and 14 stand finally rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Ogushi et al. (JP 59078124, 1984). According to the Examiner, Ogushi et al. teach a pharmaceutical formulation comprising EPO adjusted to a pH of 5-8 with tris-(hydroxymethyl)-aminomethane ("Tris").

Applicants respectfully disagree with the Examiner's characterization of the Ogushi reference. From the limited information provided (i.e., the English abstract), it appears that Ogushi teaches a method of extracting EPO from a fluidic biological sample, for example "urine, blood plasma, or a placental extract, in particular preferably urine and blood plasma obtained from a patient with anemia", such method including an initial step of adjusting the fluid sample to a pH of 5 to 8 using with Tris. According to Ogushi, the Tris-treated biological fluid sample is then reacted with ammonium sulfate to yield a precipitate that contains EPO. The EPO precipitate may then be subsequently recovered, filtered and purified to yield "erythropoietin if [sic] good quality containing no CS factor".

Applicants respectfully submit that Ogushi's Tris-treated sample of biological fluid cannot be fairly characterized as a "stable pharmaceutical formulation of EPO", much less a stable pharmaceutical formulation that "does not contain amino acids or human serum albumin". HSA is the most abundant protein in human blood plasma and therefore would necessarily be present in a Tris-treated sample of blood plasma. Likewise, urine typically includes amino acids, for example, alanine, carnosine, glycine, and histidine, in addition to proteins, enzymes, vitamins, and other organic materials; a urine sample from a patient with anemia is likely to be contaminated with blood products as well. In fact, it is unlikely that any native biological fluid sample can be characterized as free from amino acids and human serum albumin as the present claims require. Thus, Applicants respectfully submit that since Ogushi's Tris-treated biological fluid sample does not meet each and every element of claim 1, it cannot anticipate the invention of the pending claims 1, 5, and 14.

Furthermore, while the "good quality" EPO that results from Ogushi's preparation

method may indeed be subsequently put to pharmaceutical use, there is no suggestion that such a downstream application would involve formulation of the obtained EPO (a) with TRIS at a pH between 5.9 and 6.8, or (b) with TRIS in the absence of amino acids and human serum albumin. As noted previously, following the guidance of the prior art, one would expect either option to result in an unsatisfactory EPO formulation and combining the two options would certainly be expected to result in failure.

Thus, Applicants respectfully submit that the present invention is neither anticipated nor rendered obvious by the teachings of Ogushi. Nevertheless, in an effort to expedite prosecution, Applicants have amended claim 1 to require a stable "phosphate-buffered" pharmaceutical formulation of EPO containing tris-(hydroxymethyl)-aminomethane as stabilizer, whereby the formulation does not contain amino acids or human serum albumin, further wherein the pH of the formulation ranges from 5.9 to 6.8. Applicants respectfully submit that Ogushi fails to disclose the addition of a phosphate buffer to their Tris-treated, EPO-containing, biological fluid sample. Applicants further submit that there is no suggestion in the art to modify the Ogushi sample to include such a phosphate buffer. As noted previously, utilizing multiple buffer systems together is both counterintuitive and unduly complex. Accordingly, while one of ordinary skill in the art may arguably be motivated to use one or the other of TRIS and phosphate to arrive at a desired pH, there is no reason to expect a combination of the two to be operable, much less to yield a pharmaceutical formulation of EPO having the previously noted unexpected degree of stability and marked reduction in aggregate formation.

In view of the above, Applicants request reconsideration and withdrawal of the rejection of claims 1, 5, and 14 under 35 U.S.C. § 102(b) as anticipated by Ogushi et al. (JP 59078124, 1984).

Espada et al.:

Claims 1, 5, and 14 stand further rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Espada et al. (Biochem. Med., 1970). According to the Examiner, Espada et al. teach a method for concentrating EPO from human urine comprising the steps of adding to the urine an

ethanolic solution of benzoic acid and then separating and dissolving the precipitate in a Tris solution adjusted to a pH of 6.3 to 6.7.

Applicants respectfully disagree with the Examiner's characterization of the Espada reference. Like Ogushi, Espada teaches a method of isolating EPO from a fluidic biological sample, more particularly concentrating EPO from human urine. The only difference is that instead of using Tris to dilute and buffer the initial sample, Espada uses an ethanol Tris solution to dissolve flakes of benzoic acid having protein material (i.e., EPO) adsorbed thereto (see step 2, p. 477), said flakes resulting from the addition of an ethanolic solution of benzoic acid to a human urine sample (see p. 477, lines 2-3). The addition of Tris results in the formation of an EPO containing precipitate that is repeatedly centrifuged and suspended to arrive at a solid material that may then be solubilized in water to give a "clear solution containing all the activity and an inactive precipitate that is about 30% of the original weight" (see step 4, p. 477). Thus, Applicants respectfully submit that like Ogushi's Tris-treated biological fluid sample, Espada's Tris-dissolved benzoic acid flakes cannot be fairly characterized as a "stable pharmaceutical formulation of EPO". Furthermore, given that human urine routinely includes amino acids, for example, alanine, carnosine, glycine, and histidine, as well as proteins, enzymes, vitamins, and other organic materials, Espada's Tris-dissolved benzoic acid flakes cannot be fairly characterized as a stable pharmaceutical formulation that "does not contain amino acids or human serum albumin" as required by the pending claims. Thus, since Espada's solution of Tris-dissolved benzoic acid flakes does not meet each and every element of claim 1, Applicants respectfully submit that it cannot anticipate the invention of the claims 1, 5, and 14.

Furthermore, while the aqueous EPO solution that results from Espada's concentration method may indeed be subsequently put to pharmaceutical use, there is no suggestion that such a downstream application would involve formulation of the obtained EPO (a) with TRIS at a pH between 5.9 and 6.8, or (b) with TRIS in the absence of amino acids and human serum albumin. As noted previously, following the guidance of the prior art, one would expect either option to result in an unsatisfactory EPO formulation and combining the two options would certainly be expected to result in failure.

Thus, Applicants respectfully submit that the present invention is neither anticipated nor rendered obvious by the teachings of Espada. Nevertheless, in an effort to expedite prosecution, Applicants have amended claim 1 to require a stable "phosphate-buffered" pharmaceutical formulation of EPO containing tris-(hydroxymethyl)-aminomethane as stabilizer, whereby the formulation does not contain amino acids or human serum albumin, further wherein the pH of the formulation ranges from 5.9 to 6.8. Applicants respectfully submit that Espada fails to disclose the addition of a phosphate buffer to their solution of Tris-dissolved benzoic acid flakes. Applicants further submit that there is no suggestion in the art to modify the Espada solution to include such a phosphate buffer. As noted previously and above, utilizing multiple buffer systems together is both counterintuitive and unduly complex. Accordingly, while one of ordinary skill in the art may arguably be motivated to use one or the other of TRIS and phosphate to arrive at a desired pH, there is no reason to expect a combination of the two to be operable, much less to yield a pharmaceutical formulation of EPO having the previously noted unexpected degree of stability and marked reduction in aggregate formation.

In view of the above, Applicants request reconsideration and withdrawal of the rejection of claims 1, 5, and 14 under 35 U.S.C. § 102(b) as anticipated by Espada et al. (Biochem. Med., 1970).

Rejections under 35 U.S.C. § 103

Ogushi or Espada in view of Cho:

Claims 9, 10, and 13 stand finally rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Ogushi or Espada as applied to claim 1, further in view of Cho et al. (USPN 5,656,289). According to the Examiner, while Ogushi and Espada fail to teach a pharmaceutical formulation comprising EPO and TRIS, together with 0.005 to 0.1% w/v polysorbate, the Cho reference cures this deficiency by teaching methods for pharmaceutical formulations comprising EPO and polysorbate 20 or polysorbate 80. The Examiner thus concludes that it would have been obvious to include the additional components disclosed by Cho in the Ogushi or Espada EPO pharmaceutical formulation to arrive at the invention presently claimed.

Applicants reiterate that neither Ogushi's Tris-treated biological fluid sample nor Espada's solution of Tris-dissolved benzoic acid flakes constitutes a solution intended for pharmaceutical application. Accordingly, one skilled in the art would not be motivated to add conventional pharmaceutical excipients, detergents, or emulsifiers, such as polysorbate surfactants, thereto. Thus, Applicants respectfully submit that the Cho reference not only fails to cure the deficiencies the Ogushi and Espada references noted above in the context of pending claim 1, but also fails to provide the requisite motivation or suggestion for the invention of claims 9, 10, and 13. Specifically, the Cho reference fails to provide a motivation to combine EPO with a TRIS stabilizer at a pH of 5.9 to 6.8 in the absence of amino acids and human serum albumin to arrive at the surprising stable pharmaceutical formulation of the pending claims. Accordingly, Applicants respectfully submit that the cited references, alone or in combination, fail to render obvious the invention of the pending claims. Thus, Applicants request reconsideration and withdrawal of the rejection of claims 9, 10, and 13 under 35 U.S.C. § 103 as obvious over Ogushi or Espada in view of Cho.

Espada in view of Konings:

Claim 12 stands rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Espada et al. as applied to claim 1, further in view of Konings et al. (USPN 5,376,632). According to the Examiner, while Espada et al. fail to teach a pharmaceutical formulation comprising EPO and TRIS, together with EDTA in an amount ranging from 0.1 to 0.5 mM, the Konings reference cures this deficiency by teaching methods for stabilizing EPO in an aqueous solution, more particularly methods for avoiding the heavy metal catalyzed degradation of EPO through the inclusion of suitable complexing agents, such as calcium chloride or EDTA, for example at a concentration ranging from 0.2 to 2 g/l (i.e., 0.1 to 0.5 mM). The Examiner thus concludes that it would have been obvious to include the additional components disclosed by Konings in the Espada EPO pharmaceutical formulation to arrive at the invention presently claimed.

Again, Applicants wish to remind the Examiner that Espada's solution of Tris-dissolved benzoic acid flakes does not constitute a solution intended for pharmaceutical application. Rather,

it represents an intermediate product in a complex concentration process, a process that involves subjecting this intermediate to multiple centrifugation and resuspension steps before yielding a final concentrated aqueous solution of EPO. Accordingly, one skilled in the art would not be motivated to add pharmaceutical excipients associated with conventional EPO formulations much less complexing agents such as EDTA or calcium chloride. In fact, one might expect such complexing agents to interfere with the downstream precipitation steps. Thus, Applicants respectfully that the Konings reference not only fails to cure the deficiencies of the Espada reference noted above in the context of pending claim 1 but further fails to provide the requisite motivation or suggestion for the invention of claim 12. Specifically, the Konings reference fails to provide a motivation to combine EPO with a TRIS stabilizer at a pH of 5.9 to 6.8 in the absence of amino acids and human serum albumin to arrive at the surprising stable pharmaceutical formulation of the pending claims. Accordingly, Applicants respectfully submit that the cited references, alone or in combination, fail to render obvious the invention of the pending claims. Thus, Applicants request reconsideration and withdrawal of the rejection of claim 12 under 35 U.S.C. § 103.

CONCLUSION

In sum, Applicants respectfully submit that the presently claimed stable, phosphate-buffered, pharmaceutical formulation of EPO is neither anticipated nor rendered obvious by the prior art of record. Accordingly, Applicants submit that pending claims 1-6 and 8-14 are in condition for allowance and respectfully petition for an early indication of such.

The outstanding Office Action set a three-month shortened statutory period for response, response being due on or before **October 18, 2008**. Accordingly, Applicant submits that this response is timely and that no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to the undersigned's Deposit Account No. **50-2101**.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: September 18, 2008

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